IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application No.	:	10/560,377
Confirmation No.	:	3823
Applicant	:	Catherine J. Pachuk
Filed	:	June 19, 2006
Title	:	Conserved HBV and HCV Sequences Useful for Gene Silencing
TC/A.U.	:	1648
Examiner	:	Bo PENG
Docket No.	:	051058-034000-US
Customer No.	:	90162

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Commissioner for Patents
Alexandria, Virginia 22313-1450

APPEAL BRIEF PURSUANT TO 37 C.F.R. § 41.37

I. IDENTIFICATION PAGE

Dear Commissioner:

This Appeal Brief is filed pursuant to 37 C.F.R. §41.37. The Appeal Brief is filed pursuant to the Appellant's appeal to the Board of Patent Appeals and Interferences ("Board") from the final rejection of claims 63-67 and 78-79 in the August 17, 2010 Final Office Action (Ex. B). An amendment under 37 C.F.R. §1.116 was filed on November 17, 2010 (Ex. C). A Notice of Appeal was filed on February 16, 2011 (Ex. D) with a Petition and fees for three months Extension of time. An Advisory Action was issued by the Examiner on April 19, 2011 (Ex. E).

Pursuant to 37 C.F.R. §41.31(a) the due date to file this Appeal Brief is two months from the Notice of Appeal filing date, *i.e.*, by April 16, 2011. Pursuant to 37 C.F.R. 1.136(a) Appellants file herewith a Petition for an Extension of Time for five months. The appropriate fee is attached herewith.

II. TABLE OF CONTENTS

III. REAL PARTY IN INTEREST

The real party in interest is Alnylam Pharmaceuticals Inc., the assignee of record, having its place of business at 300 Third Street, Third Floor, Cambridge, MA 02142.

IV. RELATED APPEALS AND INTERFERENCES

There are no other appeals or interferences that will directly affect, be directly affected by, or have a bearing on the Board of Patent Appeals and Interferences in the present appeal.

V. STATUS OF CLAIMS

Claims 1-62, 68-77, and 80-97 have been cancelled. Claims 98-101 are withdrawn as being directed to a non-elected invention. Claims 63-67, 78, and 79 are currently pending and are finally rejected. This appeal is taken from the final rejection of claims 63-67, 78, and 79. No claims have been allowed.

VI. STATUS OF AMENDMENTS

An Amendment under 37 C.F.R. 1.116 (Ex. C) was submitted on August 17, 2010 subsequent to the Final Office Action dated August 17, 2010 (Ex. B). An Advisory Action issued on April 19, 2011 (Ex. E), indicating that the Amendment under 37 C.F.R. 1.116 filed on August 17, 2011 was entered but did not place the claims in condition for allowance.

VII. SUMMARY OF CLAIMED SUBJECT MATTER

Pursuant to 37 C.F.R. § 41.37 (c)(1)(v), exemplary references to the specification and drawings (Ex. A) are included in the below summary of the independent claims. Such references are by way of example only and are not to be construed in a limiting manner.

Claims 63 and 78 are the rejected independent claims. The claims relate to a composition (claim 78) for inhibiting expression of a Hepatitis B virus polynucleotide in an *in vivo* mammalian cell comprising a double-stranded RNA effector molecule that comprises an at least 19 contiguous base pair nucleotide sequence in a double stranded conformation from within a sequence selected from the group consisting of SEQ ID NO: 3 and SEQ ID NO: 10, wherein U is substituted for T, and a method of administering the same to an *in vivo* mammalian cell (claim 63).

Independent Claim 63

Claim 63 is directed to a method of inhibiting expression of a Hepatitis B virus polynucleotide in an *in vivo* mammalian cell comprising administering to the cell a double-stranded RNA effector molecule (page 19, lines 15-20, Ex. A) that comprises an at least 19 contiguous base pair nucleotide sequence (page 3, line 29 continuing to page 4, line 1, and page 24, lines 12-18, Ex. A) in a double stranded conformation (page 20, lines 14-16, Ex. A) from within a sequence selected from

the group consisting of SEQ ID NO: 3 and SEQ ID NO: 10, wherein U is substituted for T (page 4, lines 1-4, Ex. A).

Independent Claim 78

Claim 78 is directed to a composition for inhibiting expression of a Hepatitis B virus polynucleotide in an *in vivo* mammalian cell comprising administering to the cell a double-stranded RNA effector molecule (page 19, lines 15-20, Ex. A) that comprises an at least 19 contiguous base pair nucleotide sequence (page 5, lines 5-8, and page 24, lines 12-18, Ex. A) in a double stranded conformation (page 20, lines 14-16, Ex. A) from within a sequence selected from the group consisting of SEQ ID NO: 3 and SEQ ID NO: 10, wherein U is substituted for T (page 5, lines 8-12, Ex. A).

VIII. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

Whether claims 63 and 78 are unpatentable under 35 U.S.C. 102(b) as being anticipated by US Patent No. 5,843,770 ("Ill et al.", Ex. F).

Whether claims 63 and 78 are unpatentable under 35 U.S.C. 102(b) as being anticipated by US Patent Application US20020155124 (now US Patent No. 6,680,069 ("Sallberg et al.", Ex. G).

Whether claims 63-67, 78, and 79 are unpatentable under 35 U.S.C. 103(a) in view of Ill et al. (Ex. F), Sallberg et al. (Ex. G), and McCaffrey et al. ("McCaffrey et al.," Ex. H).

IX. ARGUMENT

A. Claims 63 and 78 Were Improperly Rejected Under 35 U.S.C. § 102(b) As Unpatentable Over Ill et al.

1. Independent claims 63 and 78

a. *Independent claims illustrated by an exemplary embodiment*

The independent claims are directed, in general, to a composition (claim 78) for inhibiting expression of a Hepatitis B virus polynucleotide in an *in vivo* mammalian cell, comprising a double-stranded RNA effector molecule, which comprises an at least 19 contiguous base pair nucleotide sequence in a double stranded conformation from within a sequence selected from the group consisting of SEQ ID NO: 3 and SEQ ID NO: 10, wherein U is substituted for T, and a method of administering the same to an *in vivo* mammalian cell (claim 63).

b. *Allegations in the Office Actions and the Advisory Action*

In the Final Office Action, the Examiner rejected claims 63 and 78 under 35 U.S.C. 102(b) as being anticipated by Ill et al. (Ex. F). The Examiner had argued that "In view of the specification, the claimed dsRNA can be in a form of double stranded DNA, DNA/RNA hybrid, single stranded DNA or RNA" (page 6, paragraph 14, Ex. I). The Examiner also alleged that:

> "Ill teaches a method of inhibiting HBV in mice using antisense SEQ ID NO: 1 of HBV viral cis-acting post-transcriptional regulatory sequences ("PREs")…The antisense SEQ ID NO: 1 of the prior art comprises 'at least

> 19 contiguous base pair nucleotide sequence of the claimed dsRNA SEQ ID NO: 10, see attached sequence alignment, wherein U is substituted for T.' In view of the definition of dsRNA recited above, Ill's antisense to PRE and the method of inhibiting HBV *in vivo* meet the limitation of the claims, therefore anticipates claims 67 and 78," (page 6, paragraph 15, *Id.*).

The Examiner further argued in regard to Appellants' amendment (Ex. J) that "One of ordinary skill in the art knows that a single stranded nucleic acid can still form a 'double-stranded conformation' when there are proper CG or AU base pars (*sic*) within its own sequence or with a target sequence," (p. 3, lines 6-9, Ex. B).

The Examiner further argued that:

> "Applicant is arguing the inherent property of dsRNA. Forming 'in a double-stranded conformation' of an RNA is an inherent property of RNA. In other words, an RNA would form 'in a double-stranded conformation', when there are proper CG or AU base pars (*sic*) within its own sequence or with a target sequence…In the present case, the claims are directed to use of a dsRNA effector molecule comprising at least 19 contiguous base pair nucleotide sequence in a double-stranded conformation from with (*sic*) SEQ ID NO: 3 or SEQ ID NO: 10," (page 4 continuing to page 5, paragraph 10, Ex. B).

The Examiner further argued that:

> "the antisense SEQ ID NO: 1 of the prior art comprises 'at least 19 contiguous base pair nucleotide sequence of the claimed dsRNA SEQ ID NO: 10. Forming a 'double-stranded conformation' is an inherent property of SEQ ID NO: 1. Since SEQ ID NO: 1 of the prior art is the antisense

sequence of SEQ ID NO: 10 of the instant application, it must have the ability to form a 'double-stranded conformation' like the instant SEQ ID NO: 1," (page 5, paragraph 10, Ex. B).

In the Advisory Action, the Examiner contended that "As indicated in the previous Office Action…the RNA of SEQ ID NO: 1 of the prior art comprises 'at least 19 contiguous base pair nucleotide sequence of the claimed dsRNA SEQ ID NO: 10'. One of ordinary skill in the art knows that RNA inherently forms 'a double-stranded conformation.'" (page 2, lines 16-19 of Continuation Sheet, Ex. E).

As discussed further below, Appellants submit that the Examiner has failed to establish that the Ill et al. reference teaches any RNA, expressly or inherently, that necessarily forms 19 contiguous base pairs in a double-stranded conformation anywhere, and particularly not from within SEQ ID NO: 3 or SEQ ID NO: 10, as required by the instant claims.

c. *Ill et al. fails to teach a double-stranded RNA of 19 contiguous base pairs in a double-stranded conformation*

Appellants submit that Ill et al. fails to expressly teach dsRNA molecules having 19 **contiguous base pairs** in a double-stranded conformation as required by instant claims 63 and 78. Appellants submit that the Ill et al. reference generally relates to the introduction of double-stranded DNA that provides the expression of single-stranded, anti-sense RNA molecules, while the invention as presently

claimed is directed to methods and compositions employing double-stranded (*i.e.*, base-paired) RNA molecules (page 5, lines 15-18, Ex. C). Appellants submit that Ill et al. does not teach administering double-stranded RNA molecules, nor does Ill et al. teach RNA effector moelcules having 19 contiguous base pairs of nucleotides present in a double-stranded conformation. Neither the antisense molecules taught by Ill et al., nor Ill et al.'s SEQ ID NO:1 in particular, necessarily have any double-stranded character, let alone a 19 contiguous base paired nucleotide sequence (page 5, lines 20-23, Ex. C).

d. *Claimed dsRNAs are not identical or substantially identical to the antisense RNAs of Ill et al.*

The Examiner alleges that the antisense SEQ ID NO: 1 of the prior art comprises "at least 19 contiguous base pair nucleotide sequence of claimed dsRNA SEQ ID NO: 10," and thus that Ill et al. anticipates the instant claims (page 5, paragraph 10, Ex. B).

Appellants submit that while the antisense HBV RNA taught by Ill et al. may form a double-stranded structure upon hybridization to its cognate HBV sense RNA, the antisense RNA that Ill et al. administers or expresses is not double-stranded nor does it comprise 19 contiguous base pairs in a double-stranded conformation (page 7, lines 16-18, Ex. C).

Further, Appellants submit that the instant claims require that the "double-stranded conformation includes at least 19 nucleotides from ***within*** a sequence

selected from the group consisting of SEQ ID NO:3 and SEQ ID NO:10," (page 7, lines 18-20, Ex. C). Appellants submit that given that SEQ ID NO: 1 of Ill et al. is 587 base pairs in length, it clearly does not fall "within" the sequence of SEQ ID NO: 3 or 10 (page 7, lines 21-22, Ex. C). Appellants further submit that the Examiner has not provided a reasonable basis for the assertion that an antisense RNA of Ill et al.'s SEQ ID NO: 1 would ***inherently*** have internal self-complementarity of at least 19 contiguous nucleotides within a sequence corresponding to either of SEQ ID NO: 3 or 10 that would be necessary for an RNA of Ill et al. to form the 19 contiguous base pair nucleotide sequence in a double-stranded conformation, as required by the instant claims (page 7, lines 22-24, Ex. C). Appellants have previously respectfully requested that the Examiner point out where such a sequence of internal self-complementarity of at least 19 contiguous nucleotides, necessary to form the 19 contiguous **base paired** nucleotide sequence, as required by the instant claims, lies (page 7, lines 24-25, Ex. C). Appellants submit that on its face, it is apparent to anyone of ordinary skill in the art that such sequence does not exist within Ill et al.'s SEQ ID NO: 1, and particularly not within any sequence corresponding to SEQ ID NO: 3 or SEQ ID NO: 10 of the instant application (page 7, lines 2-8, Ex. C).

e. *Double Stranded Conformation is Not an Inherent Property of Any RNA Sequence*

The Examiner has alleged that formation of a double-stranded conformation is an "inherent property of RNA," and that an RNA forms a double-stranded conformation "when there are proper CG or AU base pars (*sic*) within its own sequence or with a target sequence" (page 4, lines 12-15, Ex. B).

Appellants submit that claims 63 and 78 require that a recited RNA effector molecule has at least 19 such contiguous **base-paired nucleotides** in a double-stranded conformation, and that an antisense RNA of SEQ ID NO: 1 does not have the internal sequence complementarity required to satisfy these limitations of claims 63 and 78, nor has the Examiner indicated any regions of SEQ ID NO: 1 that have internal sequence complementarity such that an RNA molecule having a region of at least 19 contiguous base paired nucleotides in a double-stranded conformation would necessarily be present in the administered or expressed molecule (page 7, lines 3-8, Ex. C).

Appellants further note that inherency is not established on the basis of possibility or probability - the allegedly inherent characteristic (i.e., at least 19 contiguous base-paired nucleotides of double-strandedness) ***must*** be present in the prior art reference to inherently anticipate the claimed invention (see In re Rijckaert, 9 F.3d 1531, 1534, 28 USPQ2d 1955, 1957 (Fed. Cir. 1993); *In re Oelrich*, 666 F.2d 578, 581-82, 212 USPQ 323, 326 (CCPA 1981); and *In re Robertson*, 169 F.3d 743, 745, 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999) (Table of Authorities Appendix) (page 7, lines 9-14, Ex. C). It is clear on its face that the

antisense RNAs taught by Ill et al. do not satisfy this standard and the Examiner has not indicated where such antisense RNA has the self-complementarity necessary to form at least 19 contiguous base paired nucleotides in a double-stranded conformation as required by the claims.

Accordingly, Appellants submit that an antisense sequence of Ill et al. does not inherently or otherwise satisfy the limitations of claims 63 and 78, and thus Ill et al. does not anticipate the claimed invention.

2. Dependent Claims 64-67, and 79

The Appellants respectfully submit that the dependent claims 64-67, and 79 are patentable over the cited art for the same reasons, set forth, *supra*, as the independent claims 63 and 78. Each of the dependent claims require the at least 19 contiguous base pair nucleotide sequence in a double-stranded conformation that is missing from Ill et al.

B. Claims 63 and 78 Were Improperly Rejected Under 35 U.S.C. § 102(b) As Unpatentable Over Sallberg et al.

1. Independent claims 63 and 78

a. *Independent claims illustrated by an exemplary embodiment*

The independent claims are directed, in general, to a composition (claim 78) for inhibiting expression of a Hepatitis B virus polynucleotide in an *in vivo*

mammalian cell comprising a double-stranded RNA effector molecule comprising an at least 19 contiguous base pair nucleotide sequence in a double stranded conformation from within a sequence selected from the group consisting of SEQ ID NO: 3 and SEQ ID NO: 10, wherein U is substituted for T, and a method of administering the same to an *in vivo* mammalian cell (claim 63).

b. *Allegations in the Office Actions and the Advisory Action*

In the Final Office Action, the Examiner rejected claims 63 and 78 under 35 U.S.C. 102(b) as being anticipated by Sallberg et al. (Ex. G). The Examiner had alleged that:

> "Sallberg teach methods of enhancing the immune response of an animal…using HBV nucleic acid-based antigen…wherein said nucleic acid-based antigens include a nucleotide sequence of HBV SEQ ID No: 14…Sallberg also teaches that a nucleic acid-based antigen can comprise at least 9-25, 25-50…or 2000-4000 consecutive nucleotides of any one of SEQ ID NO: 14 or an RNA that corresponds to these sequences" (page 6, paragraph 17, Ex. I).

The Examiner further argued that the nucleic acid based antigen of SEQ ID NO: 14 of Sallberg et al. is in the form of double-stranded DNA and "can form DNA/RNA hybrids…*in vivo*" and that thus the HBV nucleic acid-based antigens of Sallberg et al. "meet the structural limitation of the claimed dsRNA effector molecules," and therefore anticipate claims 63 and 78 (page 7, paragraph 18, *Id.*). The Examiner further alleged that Appellants' argument was not persuasive for the same reasons

set out in the rejection over Ill et al. (page 5, paragraph 12, Ex. B). The Examiner alleged that:

> "Sallberg has inherently taught the claimed dsRNA of SEQ ID NO: 3, because he has disclosed the nucleic acid-based antigen SEQ ID NO: 14, which comprises 'a double-stranded RNA effector molecule **comprising** an at least 19 contiguous base pair nucleotide sequence…SEQ ID NO: 3, wherein U is substituted for T'" (page 6, paragraph 14, Ex. B).

The Examiner further argued that the instant specification defines that the "claimed dsRNA molecule can be in the form of a double stranded DNA, DNA/RNA hybrid, or a single stranded RNA," and because "the HBV nucleic acid-based antigen comprising SEQ ID NO: 14…is in the form of a double stranded DNA, DNA/RNA hybrid, or mRNA (a single stranded RNA)," the HBV nucleic acid-based antigens meet the structural limitations of the claimed dsRNA effector molecules" (p. 6, paragraph 14, Ex. B).

In the Advisory Action, the Examiner contended that "Given that an RNA of SEQ ID NO: 14 has same sequence as the instant SEQ ID NO: 3, one of ordinary skill in the art would understand that the RNA of prior art would inherently form a double-stranded conformation as the RNA of the instant claims" (page 3, lines 11-14 of Continuation Sheet, Ex. E).

As discussed in further detail below, Appellants submit that the Examiner has failed to establish that the HBV nucleic acid-based antigen taught by Sallberg et al. necessarily has or can necessarily form an RNA molecule with 19 contiguous

base pairs in a double-stranded conformation from within SEQ ID NO: 3 or SEQ ID NO: 10, as required by the instant claims.

c. *Sallberg et al. fails to teach a double-stranded RNA of 19 contiguous base pair nucleotides in a double-stranded conformation*

Appellants submit that Sallberg et al. fails to teach dsRNA molecules having 19 **contiguous base pairs** in a double-stranded conformation as required by instant claims 63 and 78. Appellants submit that the nucleic acid-based antigen of the Sallberg et al. reference is not a dsRNA molecule, and that the Sallberg et al. reference does not teach (expressly or inherently) or suggest the use of an RNA molecule having at least 19 contiguous nucleotides in a double-stranded conformation, as required by instant claims 63 and 78 (page 7, lines 15-16, Ex. J).

Appellants submit that the Examiner appears to assume that SEQ ID NO: 14 and its fragments, which the Examiner has admitted are in the form of double-stranded DNA, are capable of forming DNA/RNA hybrids, or mRNA (a single stranded RNA) *in vivo*. Based on this apparent assumption, the Examiner has asserted that the HBV nucleic acid-based antigens of the Sallberg et al. reference meet the structural limitations of the dsRNA effector molecules recited in the claims (page 9, lines 1-5, Ex. C).

Appellants submit that the definition of dsRNA in the instant specification at paragraph [0049] indicates that the claimed dsRNA agent acts through a dsRNA-

mediated gene silencing or RNAi mechanism (page 8, lines 20-31, Ex. C). Appellants submit that double-stranded DNA is neither a dsRNA, *i.e.*, permits dsRNA-mediated gene silencing, nor does double-stranded DNA mediate RNAi. It is clear from the definition in the instant specification that, contrary to the Examiner's argument, double-stranded DNA is not encompassed by the term "dsRNA effector molecule" (page 8, lines 31-33, Ex. C). Further, whether the double-stranded DNA of Sallberg et al. can form DNA/RNA hybrids is irrelevant to the rejection, since Sallberg et al. does not teach or suggest that such DNA/RNA hybrids are administered or formed, particularly *in vivo*. One of skill in the art would understand that double-stranded DNA does not typically generate a DNA/RNA hybrid *in vivo.* Similarly, while Appellants agree that under the proper conditions, double-stranded DNA can be transcribed *in vivo* to produce a single-stranded mRNA, Appellants submit that such mRNAs do not have the **19 base pairs** of double-stranded character required of the dsRNA recited in the instant claims (page 9, lines 6-13, *Id.*). Further, Sallberg et al. does not teach (expressly or inherently) or suggest the use of dsRNA effector molecules that act through an RNAi mechanism or a dsRNA-mediated gene silencing mechanism as required by effector molecules satisfying the definition of the term "dsRNA" (page 9, lines 13-16, *Id.*). Accordingly, Appellants submit that Sallberg et al. does not anticipate the invention as presently claimed.

2. Dependent Claims 64-67, and 79

The Appellants respectfully submit that the dependent claims 64-67, and 79 are patentable over the cited art for the same reasons, set forth, *supra*, distinguishing the independent claims 63 and 78.

C. Claims 63-67, 78, and 79 Were Improperly Rejected Under 35 U.S.C. § 103(a) Over Ill et al., Sallberg et al., and McCaffrey et al.

1. Independent claims 63 and 78

a. *Independent claims illustrated by an exemplary embodiment*

The independent claims are directed, in general, to a composition (claim 78) for inhibiting expression of a Hepatitis B virus polynucleotide in an *in vivo* mammalian cell comprising a double-stranded RNA effector molecule comprising an at least 19 contiguous base pair nucleotide sequence in a double stranded conformation from within a sequence selected from the group consisting of SEQ ID NO: 3 and SEQ ID NO: 10, wherein U is substituted for T, and a method of administering the same to an *in vivo* mammalian cell (claim 63).

b. *Allegations in the Office Actions and the Advisory Action*

In the Final Office Action, the Examiner rejected claims 63-67, 78, and 79 under 35 U.S.C. 103(a) as being unpatentable over Ill et al. (Ex. F), Sallberg et al. (Ex. G), and McCaffrey (Nature Biotechology, 21(6):639-644; published online

May 12, 2003; "McCaffrey et al.," Ex. H). The Examiner had alleged that "Claims 63 and 78 have been summarized *supra*. Claims 64-67 require a composition comprising two dsRNAs SEQ ID NOs: 3 and 10 and a method of inhibiting HBV *in vivo* using dsRNAs SEQ ID NOs: 3 and 10," that "Ill teaches that the antisense construct is an expression plasmid encoding **one** or **more** antisense transcripts," but however that "Ill does not teach that use of two dsRNA comprises an at least 19 contiguous base pair nucleotide sequence from within SEQ ID NO: 3 and 10" (page 6, paragraphs 21-23, Ex. I). The Examiner further argued that:

> "McCaffrey teaches RNAi (dsRNA) can be applied to inhibit production of HBV replicative intermediates both in cell culture and in mice…McCaffrey shows that each shRNA targets the HBV pregenomic RNA, as well as the mRNA for the core antigen and the polymerase, and the X region and its transcript, and can inhibit HBV in cell cultures…McCaffrey shows that RNAi effectively inhibited replication initiation in cultured cells and mammalian liver, suggesting that such an approach could be useful in the treatment of viral diseases" (page 8 continuing to page 9, paragraph 25, Ex. I).

The Examiner further alleged that "the prior art has provided a finite number of predictable potential solutions for the claimed method of inhibiting HBV *in vivo* using dsRNA molecules," arguing that:

> "Ill teaches that an expression plasmid encoding **one** or **more** antisense transcripts (dsRNA effector molecule), which comprises the claimed SEQ ID NO: 10, can inhibit HBV production in mice. Sallberg teaches HBV nucleic acid-based antigen SEQ ID NO: 14, and its fragments, which

> comprises the claimed dsRNA effector molecule comprising SEQ ID NO: 3, can be used for inhibiting HBV *in vivo*. McCaffrey shows that each shRNA (dsRNA) targets the HBV pregenomic RNA, as well as the mRNA for the core antigen and the polymerase, as well as the X region and its transcript, can inhibit HBV in cell culture. McCaffrey also demonstrated that dsRNA is capable of inhibiting HBV replication in mice effectively inhibited replication initiation in cultured cells and mammalian liver, suggesting that such an approach could be useful in the treatment of viral diseases" (page 9 continuing to page 10, paragraph 27, Ex. I).

The Examiner concludes that "those of ordinary skill in the art would have had a reasonable expectation of success in using two dsRNA comprising SEQ ID NO: 3 and 10 for inhibiting HBV *in vivo*," and that "it would have been obvious to make such dsRNA effector molecules for inhibiting HBV *in vivo*" (page 10, paragraph 27, Ex. I).

The Examiner argued that Appellants' arguments against McCaffrey are not persuasive and states "First, the cited Ill and Sallberg references teach dsRNA effector molecules comprising at least 19 contiguous base pair nucleotide sequence in a double-stranded conformation from with (*sic*) SEQ ID NO: 3 or SEQ ID NO: 10" (page 7, paragraph 19, Ex. B). The Examiner reiterates, in response to Appellants' arguments (Ex. J), that:

> "Ill teaches that an expression plasmid encoding one or more antisense transcripts (dsRNA effector molecule), which comprises the claimed SEQ ID NO: 10, can inhibit HBV production in mice. Sallberg teaches HBV nucleic acid-based antigen SEQ ID NO: 14, and its fragments, which

comprises the claimed dsRNA effector molecule comprising SEQ ID NO: 3, can be used for inhibiting HBV *in vivo*. McCaffrey shows that each shRNA (dsRNA) targets the HBV pregenomic RNA, as well as the mRNA for the core antigen and the polymerase, as well as the X region and its transcript, can inhibit HBV in cell cultures. McCaffrey also demonstrated that dsRNA is capable of inhibiting HBV replication in mice" (page 7 continuing to page 8, paragraph 20, Ex. B)

In the Advisory Action, the Examiner contended that:

"Applicant's arguments against the Ill et al. and Sallberg et al. reference have been found not persuasive above. Applicant's arguments against McCaffrey alone is not persuasive, either, because the cited Ill and Sallberg references teach dsRNA effector molecules comprising at least 19 contiguous base pair nucleotide sequence in a double-stranded conformation from with (*sic*) SEQ ID NO: 3 or SEQ ID NO: 10" (page 3, lines 27-31 of Continuation Sheet, Ex. E).

As discussed below, Appellants submit that the Examiner has failed to establish that the proposed combination of Ill et al., Sallberg et al., and McCaffrey et al. teach all elements of the invention claimed in claims 63-67, 78, and 79, and, as such, fail to render the claimed invention obvious.

c. *The combination of Ill et al., Sallberg et al., and McCaffrey et al. fails to teach a double-stranded RNA of 19 contiguous base paired nucleotides in a double-stranded conformation*

Appellants submit that the term "dsRNA" does not encompass single stranded RNA in a single-stranded conformation (page 8, lines 2-3, Ex. J), and that

single-stranded antisense RNA (Ill et al.) and double-stranded DNA antigens (Sallberg et al.) are not dsRNA molecules as defined in the instant specification (page 8, lines 10-11, *Id.*). Further, Appellants reiterate that neither the Ill et al. nor the Sallberg et al. reference teaches dsRNA effector molecules corresponding to any sequence, much less double stranded RNA comprising at least a **19 contiguous base pair** nucleotide sequence in a double-stranded conformation from within a sequence selected from the group consisting of SEQ ID NO: 3 and SEQ ID NO: 10, wherein U is substituted for T, as required by the instant claims (page 8, lines 6-10, *Id.*).

Appellants submit that there is nothing in Ill et al. to indicate that SEQ ID NO: 1 or any single-stranded antisense RNAs that Ill et al. describe form a dsRNA molecule as defined by the instant claims (page 9, line 29 continuing to page 10, line 1, Ex. C). That is, the reference does not literally or inherently teach a dsRNA agent that acts through a dsRNA-mediated gene silencing or RNA mechanism (page 8, lines 20-31, *Id.*). Similarly, Appellants submit that the double-stranded DNAs of Sallberg et al. are not dsRNA molecules that anticipate the invention as presently claimed (page 10, lines 1-2, *Id.*). Accordingly, Appellants submit that there is nothing in Ill et al. or Sallberg et al. that teaches or suggests the use of dsRNA molecules that act through a dsRNA-mediated gene silencing method as required by the definition of dsRNA in the instant specification (page 10, lines 2-5, *Id.*).

Appellants further submit that McCaffrey et al., while it may teach double stranded RNA in the context of HBV inhibition, does not teach the use of a dsRNA comprising **at least 19 contiguous base pairs** of nucleotide sequence in a double-stranded conformation from within a sequence selected from the group consisting of SEQ ID NO: 3 and SEQ ID NO: 10 (page 10, lines 6-9, Ex C). Appellants note that SEQ ID NO: 3 corresponds to conserved region 3, and SEQ ID NO: 10 is a sub-sequence within SEQ ID NO: 3 (page 10, lines 11-12, *Id.*). In other words, Appellants submit that McCaffrey et al. does not teach targeting conserved region 3 as disclosed in the instant specification (page 10, lines 10-11, *Id.*).

Accordingly, Appellants submit that the proposed combination of Ill et al., Sallberg et al. and McCaffrey et al. fails to teach all elements of the invention claimed in claims 63-67, 78, and 79, and, as such, the cited combination fails to and cannot render the claimed invention obvious.

d. *The combination of Ill et al., Sallberg et al., and McCaffrey et al. does not set out a finite number of predictable solutions for the inhibition of HBV in vivo using dsRNA molecules*

The Examiner has cited from *KSR International Co. v. Teleflex Inc.* (82 U.S.P.Q. 2d1385, 2007) to support a conclusion of obviousness and argued that 'the prior art provides a finite number of identified predictable potential solutions

for the claimed method of inhibiting HBV *in vivo* using dsRNA molecules" (page 9, paragraphs 26 and 27, Ex. I).

Appellants submit that this conclusion is inappropriate for several reasons. First, Appellants submit that because the Ill et al. and Sallberg et al. references do not relate to double-stranded RNAs, as explained *supra*, they do not set out or define a finite number of identified predictable potential solutions to the problem of identifying double-stranded RNA inhibitors of HBV. Similarly, the possibility that a double-stranded DNA sequence, such as those described by Sallberg et al., can express an antigen that stimulates an immune response to HBV does not in any way relate to whether a dsRNA derived from the same sequence will inhibit viral expression or replication (page 8, line 35 to page 9, line 4, Ex. J).

Next, Appellants submit that McCaffrey et al. does not teach the use of a dsRNA comprising **at least 19 contiguous base pair** nucleotide sequence in a double-stranded conformation from within a sequence selected from the group consisting of SEQ ID NO: 3 and SEQ ID NO: 10, as evidenced by the BLAST sequence alignments of the seven sequences taught by McCaffrey et al. with SEQ ID NOs 3 and 10 (page 9, lines 8-9, Ex. J citing Ex. K). In other words, Appellants submit that McCaffrey et al. does not teach targeting SEQ ID NO: 3, disclosed in the instant specification as corresponding to conserved region 3, and SEQ ID NO: 10, which is a sub-sequence within SEQ ID NO: 3 (page 9, lines 9-11, Ex. J).

Further, Appellants submit that data provided in the instant specification show high effectiveness of five different dsRNAs (i.e., SEQ ID NOs 18-22) directed to conserved region 3 and its SEQ ID NO: 10 sub-region in reducing HBsAg in culture by at least 87% relative to control (page 9, lines 12-24, Ex. J). In contrast and importantly, examination of the data presented in the McCaffrey et al. reference shows a wide range of efficacy with the sequences they did use, and that only two of the seven sequences tried in their experiments were particularly effective in inhibiting HBV surface antigen expression in vivo and in culture (page 9, lines 25-28, *Id.*). In other words, the McCaffrey et al. reference demonstrates unpredictability with respect to the sequences that will or will not work as dsRNA inhibitors of HBV because not all of the sequences tried by McCaffrey et al. were effective (page 9, line 29 continuing to page 10, line 2, *Id.*). Appellants further submit that not only does McCaffrey et al. **not** support a predictable outcome, the reference does not provide a finite number of identified, predictable solutions to the problem of HBV inhibition *in vivo*. Appellants submit that the broad range of different target sequences, combined with a range of potential different dsRNA sizes against a virus demonstrated to provide unpredictable inhibition with RNAi supports a different conclusion (page 10, lines 4-8, *Id.*). In fact, the McCaffrey et el. sequence HBVU6no.1 did not very effectively reduce HBV expression despite targeting a sequence very close on the HBV transcripts to that sequence targeted

more effectively by HBVU6no.2 (see, for example, McCaffrey et al.'s Figures 1 and 2) (page 10, lines 8-11, *Id.*).

Accordingly, Appellants submit that the cited prior art does not support the predictable ability to target HBV using dsRNA, and thus cannot support the conclusion of obviousness drawn in the Office Action regarding the subject claims.

2. Dependent Claims 64-67, and 79

The Appellants respectfully submit that the dependent claims 64-67, and 79 are patentable over the cited art for the same reasons, set forth, *supra*, for the independent claims 63 and 78.

X. CONCLUSION

For at least the foregoing reasons, the rejection of appealed claims 63-67, 78, and 79 set forth in the Final Office Action dated August 17, 2010 and Advisory Action dated April 19, 2011, should be reversed.

Respectfully submitted,

Date: September 16, 2011

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XI. INDEX TO THE APPENDICES

SUBJECT	EXHIBIT
CLAIM APPENDIX	
EVIDENCE APPENDIX	
LIST OF EVIDENCE	
PCT/US2004/019299	A
Final Office Action dated August 17, 2010	B
Amendment dated November 17, 2010	C
Notice of Appeal filed February 16, 20100	D
Advisory Action dated April 19, 2011	E
U.S. Patent No. 5,843,770 (Ills et al.)	F
U.S. Patent Application Publication No. 20020155124, now U.S. Patent No. 6,680,059 (Sallberg et al.)	G
McCaffrey et al. (Nat. Biotech., 21(6):639-644, 2003	H
Office Action dated September 4, 2009	I
Amendment dated December 4, 2009	J
Following were entered into the Record by Examiner in Ex. J:	
BLAST comparison of SEQ ID NO: 3 and SEQ ID NO: 10 against McCaffrey et al. sequences	K
TABLE OF AUTHORITIES APPENDIX	
RELATED PROCEEDINGS APPENDIX	

XII. CLAIMS APPENDIX

CLEAN COPY OF CLAIMS ON APPEAL

A copy of the pending claims involved in the appeal, including the correct claim identifiers, is provided below.

1-62. (CANCELLED)

63. (REJECTED) A method for inhibiting expression of a polynucleotide sequence of hepatitis B virus in an in vivo mammalian cell comprising administering to said cell a double-stranded RNA effector molecule comprising an at least 19 contiguous base pair nucleotide sequence in a double-stranded conformation from within a sequence selected from the group consisting of SEQ ID NO:3 and SEQ ID NO:10; wherein U is substituted for T.

64. (REJECTED) The method of claim 63, wherein at least two of said double-stranded RNA effector molecules are administered to the same mammalian cell.

65. (REJECTED) The method of claim 64, wherein said at least two double-stranded RNA effector molecules comprise an at least 19 contiguous base pair nucleotide sequence in a double-stranded conformation from within SEQ ID NO:3 and SEQ ID NO:10.

66. (REJECTED) The method of claim 65, wherein said administering is accomplished by providing one or more expression vectors capable of expressing in said mammalian cell said at least two double-stranded RNA effector molecules.

67. (REJECTED) The method of claim 66, wherein said one or more expression vectors further comprise a promoter selected from an RNA polymerase I promoter, an RNA polymerase II promoter, a T7 polymerase promoter, an SP6 polymerase promoter, an RNA polymerase III promoter, a tRNA promoter, and a mitochondrial promoter, said promoter operably linked to a sequence encoding at least one of said double-stranded RNA effector molecules.

68-77. (CANCELLED)

78. (REJECTED) A composition for inhibiting the expression of a polynucleotide sequence of hepatitis B virus in an in vivo mammalian cell comprising a double-stranded RNA effector molecule, comprising an at least 19 contiguous base pair nucleotide sequence in a double-stranded conformation from within a sequence selected from the group consisting of SEQ ID NO:3 and SEQ ID NO:10; wherein U is substituted for T.

79. (REJECTED) The composition of claim 78 comprising at least two double-stranded RNA effector molecules wherein said effector molecules comprise an at least 19 contiguous base pair nucleotide sequence in a double-stranded conformation from within SEQ ID NO:3 and SEQ ID NO:10.

80-97. (CANCELLED)

98. (WITHDRAWN) The method of claim 63, wherein said double-stranded RNA effector molecule comprises a sequence selected from the group consisting of SEQ ID NOs 18-22 where U is substituted for T.

99. (WITHDRAWN) The method of claim 98 wherein expression of said double-stranded RNA effector molecule in an HBV cell culture transfection assay mediates at least 87% inhibition of HBsAg level relative to control lacking said effector molecule.

100. (WITHDRAWN) The composition of claim 78 wherein said double-stranded RNA effector molecule comprises a sequence selected from the group consisting of SEQ ID NOs 18-22 where U is substituted for T.

101. (WITHDRAWN) The composition of claim 100 wherein expression of said double-stranded RNA effector molecule in an HBV cell culture transfection assay mediates at least 87% inhibition of HBsAg level relative to control lacking said effector molecule.

XIII. EVIDENCE APPENDIX

The evidence relied on in this brief was entered into the record at least in the Final Office Action dated August 17, 2010 and Advisory Action dated April 19, 2011. The remaining documents are entries in the file history and they speak for themselves and are provided for the convenience of the Board.

LIST OF EVIDENCE

	EXHIBIT
PCT/US2004/019229	A
Final Office Action dated August 17, 2010	B
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U.S. Patent No. 5,843,770 (Ills et al.)	F
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McCaffrey et al. (Nat. Biotech., 21(6):639-644, 2003	H
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BLAST comparison of SEQ ID NO: 3 and SEQ ID NO: 10 against McCaffrey et al. sequences	K

XIV. TABLE OF AUTHORITIES APPENDIX

In re Rijckaert, 9 F.3d 1531, 1534, 28 USPQ2d 1955, 1957 (Fed. Cir. 1993)

In re Oelrich, 666 F.2d 578, 581-82, 212 USPQ 323, 326 (CCPA 1981)

In re Robertson, 169 F.3d 743, 745, 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999)

KSR International Co. v. Teleflex Inc. (82 U.S.P.Q. 2d1385, 2007)

XV. RELATED PROCEEDINGS APPENDIX

None.